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Cytoreductive therapy in the era of targeted therapies: a review

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Abstract:

In the pre-targeted therapy era, palliative cytoreductive nephrectomy combined with cytokine immunotherapy was the standard treatment protocol for the management of metastatic renal cell carcinoma. The introduction of targeted therapies has improved response rates, median survival and overall prognosis when compared to immunotherapy. The role of cytoreductive nephrectomy in providing an independent survival advantage when used alongside immunotherapy has been demonstrated by two randomised controlled trials. However, with the new shift in improved treatment outcomes from cytokine immunotherapy to targeted therapies, the continuing role of cytoreductive nephrectomy as a viable surgical treatment modality remains controversial.

Keywords:

Cytoreductive nephrectomy, tyrosine kinase inhibitors, immunotherapy

Introduction:

Renal cell carcinoma (RCC) is the 12th most common cancer worldwide and the third leading cause of mortality amongst genitourinary malignancies, representing a significant health burden [1]. In 2012, RCC was associated with an annual incidence of 338,000 cases globally and a mortality rate of 2% [2]. Interestingly, despite the increase of incidental carcinomas detected on radiological imaging approximately, 25% of patients with RCC present with metastases at the time of diagnosis[3]. Furthermore, between 20-40% of patients undergoing nephrectomy for localised RCC will go on to develop metastatic disease [4].Historically, patients with disseminated disease had a dismal prognosis with an estimated 5 year survival rate of less than 5% and a median survival time of 6 to 10 months [5]. Over the last decade with the advent of novel targeted therapies 5 year survival rates have increased modestly to 8% [1].

In the pre-targeted therapy era, evidence based on two significant prospective randomised trials confirmed the role of cytoreductive nephrectomy (CN) in the management of metastatic RCC (m-RCC) in conjunction with adjuvant immunotherapy. Proposed benefits of CN include debulking of the primary tumour which acts to stimulate the immune system to control residual disease as well as removal of the source of potential new metastases[6].

In the past two decades the von-Hippel-Lindau (VHL) gene, a tumour suppressor gene has been identified as an important step in renal carcinogenesis. A loss of VHL function, results in the accumulation of hypoxia-inducible factor (HIF), culminating in increased expression of pro-angiogenic growth factors including vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and pigment epithelial derived factor (PEDF). These growth factors result in increased cell proliferation, survival and angiogenesis [7]. Thus, inhibition of growth factor signalling pathways, by the introduction of targeted therapies represents a novel strategy in the management approach tom-RCC. The efficacy of targeted therapies has been evaluated within numerous randomised phase III trials [8,9,10,11]. Overall, prolonged median survival and reduced toxicity when compared to

immunotherapy, have helped establish its central role in treatment protocols[12]. Whether a continuing surgical approach to m-RCC management fits into this new treatment paradigm and translates into improved treatment outcomes remains to be elucidated.

Role of targeted therapy in metastatic renal cell carcinoma:

Currently licensed targeted therapies approved for use in m-RCC include three multi-targeted TKI's: sunitinib, sorafenib and paopanib as well as newer more potent agents axitinib and tivozanib. Other targeted agents include VEGF monoclonal antibody, known as bevacizumab and mammalian target of rapamycin (mTOR) inhibitor, temsirolimus and everolimus [13].

By exploiting the molecular differences between tumour cells and healthy tissues, these agents offer a targeted tumour response resulting in improved treatment outcomes when compared to immunotherapy. Despite variations in treatment and tolerability outcomes, most randomised phase III trials reveal superior response rates, progression free survival (PFS) and overall survival (OS)[8,9,10,11]. Sunitinib demonstrated a therapeutic advantage over INF- α 2b with PFS of 26.4 months compared to 21.8 months[8]. Sorafenib, a raf kinase and VEGF inhibitor, revealed superior outcomes in OS when compared to placebo in patients with cytokine refractory m-RCC (17.3 months vs 14.8 months respectively) [9]. Disappointingly bevacizumab, used in combination with INF- α 2b, offered marginal prolonged OS when compared with INF- α 2b alone with a median duration of 18.3 months and 17.4 months, respectively which was not statistically significant. [10]. Similarly, although temsirolimus demonstrated superior OS compared to INF- α 2b alone (10.9 months vs 7.3 months) this was only observed on secondary analysis [11].

These agents are generally considered relatively safe, associated with improved adverse effect profile compared to cytokine therapy including toxicity related effects as well as systemic symptoms including fever, loss of appetite, malaise and diarrhoea [12]. Moreover, targeted therapies have demonstrated equally efficacious treatment outcomes when using lower doses of cytokine therapy as a combined treatment strategy, thereby improving overall safety and tolerability outcomes [13].

Overall, the introduction of targeted therapies have largely superseded immunotherapy within the metastatic setting. Despite superior outcomes associated with targeted therapies patient response rates remain modest from 10-15% to up to 40%, translating into marginal improvements in 5 year survival rates [14]. Unfortunately their clinical response is not permanent and time to progression of disease is on average between 6-12 months [15]. Furthermore, it is important to bear in mind the majority of participants receiving systemic therapy, may also have undergone prior CN, thus the survival benefit conferred by such therapies may not be independent of its use [16]. In addition, the primary endpoints assessed in such trials were objective parameters such as OS and PFS. However, prolongation of survival without an associative improvement in the health related quality of life (HRQL) although clinically advantageous, may not be valued by every patient and their families. HRQL outcomes and patients perception of positive treatment outcomes often directly impact on patient's decision to continuing further care. As a clinical being

mindful of such factors is a key principal when counselling patients on therapeutic options available [17].

Role of cytoreductive nephrectomy in metastatic renal cell carcinoma:

The exact pathophysiological mechanisms explaining the rationale of CN in treatment protocols remain unclear. Primarily, CN is thought to result in a significant reduction in disease burden and development of new metastasis, thereby extending the time to lethal tumour metastasis.

Elucidation of renal cell carcinogenesis reveals it is essentially an immunogenic tumour manipulating the function of the immune system, resulting in suppression of the anti-tumour effect exhibited by our defence mechanism. During this process the primary tumour is believed to resist exogenous growth inhibitory signals, evade apoptosis and recruit angiogenic factors signals, whilst diverting the circulating immune system away from metastatic sites to avoid immunosurveillance [18] Numerous mechanistic properties of CN have been proposed including removal of these pro-angiogenic factors and removal of suppression of immunological factors which manipulate residual disease [19].

Studies have also described CN to result in a low grade systemic acidosis, acting to disrupt the tumour microenvironment and halting metastatic growth [20]. Cellular mechanisms aside, CN can result in symptomatic benefit in multiple ways. These include pain relief, management of intractable haematuria, uncontrolled hypertension as well as control of refractory hypercalcaemia [21]. The psychological impact of removing the primary tumour may also improve HRQL and perception of positive treatment outcomes [22].

Interestingly, early reports demonstrated that up to 1% of patient's experienced spontaneous regression of metastatic disease following CN. Despite this promising finding, further studies suggest it to be a fortuitous event [6]. Due to the rarity of such cases the pathophysiological mechanisms responsible for regression remain unclear and indeed identifying potential candidates for regression, impossible. However it has been speculated that spontaneous regression may result in removal of growth factors secreted by the tumour as well as promotion of apoptosis [23].

Cytoreductive therapy in the era of cytokine immunotherapy:

To date, two prospective randomised trials comparing CN and adjuvant immunotherapy versus immunotherapy alone, support the multidisciplinary paradigm of performing CN for the management of m-RCC. In 2001, the European Organisation for the Research and Treatment of Cancer (EORTC) study compared palliative nephrectomy alongside INF- α immunotherapy with INF- α monotherapy in m-RCC patients. Patients randomised to undergo surgical intervention had an independent survival benefit when compared to immunotherapy with a median duration of survival of 17 months and 7 months, respectively. Furthermore, PFS was prolonged in nephrectomised patients to 5 months compared to 3 months in those receiving immunotherapy alone [24]. Outcomes from a larger trial of 241 participants, led by the Southwest Oncology group (SWOG 8949)

demonstrated a less pronounced 3 month median survival advantage in participants who underwent CN prior to INF- α 2b therapy with a median survival of 11.1 months compared to 8 months in participants receiving INF- α 2b therapy alone [25].

A pooled analysis of both the EORTC and SWOG trials led by Flanigan et al reported overall median survival was superior in CN with INF- α 2b at 13.6 months compared to 7.8 months with INF- α 2b alone [26]. Of note, the difference in median survival was independent of pre-defined clinical variables such as PS, metastatic site and presence or absence of metastatic lesion. Following the original publication, data based on a 9 year follow-up concluded superior OS of 11 months versus 8 months in patients undergoing CN compared to immunotherapy alone. The hazard ratio in nephrectomised patients was 0.74, representing a 26% reduction in death. Interestingly, the hazard ratio in these patients when categorised according to PS, metastatic site and presence of metastatic lesion was also less than 1, supporting the author's recommendation of performing CN in all surgically appropriate candidates [27]. Whether prognostic factors identified in the immunotherapy era will be similar within the targeted therapy setting is debatable and requires further investigation. Currently the CARMENA trial assessing CN with adjuvant sunitinib versus sunitinib monotherapy is underway where it is hoped assessment of pre-defined clinical factors would provide conclusive information on predicting treatment outcomes [28].

Drawbacks and limitations of these historic trials have led to controversy regarding the ongoing role of CN in m-RCC management. Firstly, a disproportionate number of patients with PS1 were assigned to the immunotherapy treatment arm compared to the CN arm, 58.9% and 46.6% respectively [29]. PS 1 is associated with an invariably worse prognosis compared to PS 0, with a study led by Elson et al revealing a median survival of 6.7 months compared to 10.1 months, respectively [30]. Secondly, both trials were significantly underpowered throwing the validity of their results and the conclusions drawn into question. Thirdly, the eligibility criteria required patients to have a PS of 0 or 1 along with evidence of resectable primary tumour. As a result, the data is limited regarding patients with unresectable primary tumour, widely disseminated disease or multiple metastases [29]. Although these shortcomings cloud the continuing role of CN, numerous, albeit retrospective studies, support the widely held opinion that CN remains beneficial in the treatment of m-RCC. A Cochrane based analysis concluded that in appropriately selected surgical patients with m-RCC, CN prior to immunotherapy provides the best survival strategy [31].

Cytoreductive nephrectomy in the era of targeted therapy:

The benefit derived from CN alongside newly developed targeted therapies remains unclear. Current evidence is based on non-randomised trials which appear promising, suggesting a possible survival advantage. A recent meta-analysis of 11 non-randomised trials evaluated a total of 39,953 patients with advanced RCC revealing patients treated with CN in addition to targeted therapies had a 54% reduced risk of death compared to targeted therapy alone [32]. One of the largest retrospective studies based on the SEER national database of 20,104 patients led by Conti et al revealed overall survival advantage

of 19 months versus 4 months in favour of patients who underwent CN [33]. Such improvements in survival benefit have been mirrored in studies varying from large national databases to large multicentre case series. Importantly, the benefit of CN was confirmed in a multivariate analysis adjusting for clinicopathological variables including age, PS and other biochemical parameters [32].

Currently no study has prospectively validated the role of CN when added to targeted therapies and as such current guidelines do not provide definitive recommendations for its use. Consequently, over the last decade there has been an increasing trend in the use of targeted therapies whilst CN adoption has fallen. A study by Psutka et al revealed the annual rate of targeted therapy utilisation from 2004-2010 increased from 10% to 98.2%. Comparatively the utilisation of CN has decreased in half from 30% to 15% with some clinicians calling for a purely systemic approach to m-RCC management in the absence of level I evidence [34].

Many argue the morbidity associated with a procedure of unknown efficacy which has the potential to delay targeted therapy, known to derive clinical benefit to be unacceptable. In a retrospective study of 30 nephrectomised patients only 23% of patients underwent systemic therapy post-operatively, whilst progression of disease, surgical morbidity and mortality precluded 77% of patients from receiving systemic therapy [35]. Although this was an extremely small case series it is important to develop criteria to ascertain which patients would benefit from CN prior to systemic therapy. Consistent with this, studies exploring prognostic factors associated with m-RCC suggest time from diagnosis to treatment to be the most significant predictive factor in determining OS [36].

Currently it remains unclear whether patients of all risk disease groups benefit from CN, however retrospective evidence suggests CN results in reduced risk of death even in poor risk groups although not to the same extent as favourable risk groups. Ultimately this may result in selection bias firstly, in identifying patients with favourable predictive factors, whom are likely to derive maximum clinical benefit and improved post-operative outcomes as potential candidates for surgery. Secondly, in selecting patients who respond positively to systemic therapy and exhibit stable disease as surgical candidates, avoiding those with early progressive disease associated with an invariably worse prognosis and treatment outcomes [37].

Patient selection in cytoreductive nephrectomy:

The identification of prognostic factors that allow patient risk stratification prior to CN is important, not only in selecting patients who would most likely derive a therapeutic advantage but also to effectively counsel patients prior to treatment, optimise post-operative recovery and maximise systemic therapy. Several prognostic models have been developed including the Memorial Sloan Kettering Cancer Centre (MSKCC) model which utilises independent predictors of poor outcomes such as elevated LDH, increased corrected calcium, low serum haemoglobin, low PS score and increased time from diagnosis to initiation of therapy [38]. Patients are subsequently categorised in risk groups

and in a study led by Motzer, the comparative median survival outcome in patients with poor versus favourable risk were 4 and 20 months, respectively [39].

Post-operative factors likely to impact on treatment outcomes have also been explored. The percentage of tumour removed; known as the fractional percentage of tumour volume removed (FPTV) has been found to be an independent predictor of PFS when the median FPTV is 95% [40]. Fallick et al demonstrated reduction of >75% of overall tumour burden was required to be beneficial [41].

There is also progress in studies aiming to identify patients with poor risk who may benefit from avoiding the potential morbidity and mortality associated with surgery and commence targeted therapy earlier. In a large retrospective study comparing pre-operative outcomes in patients undergoing CN or systemic monotherapy, Culp et al identified seven pre-operative negative predictors of survival. These include low serum albumin, high serum LDH, clinical tumour classification of T3 or T4 disease, symptoms at presentation caused by metastatic disease, presence of liver metastasis and radiological evidence of retroperitoneal or supra-diaphragmatic lymphadenopathy at time of CN. They concluded patients who had more than 4 risk factors did not benefit from CN versus systemic therapy alone [42].

Recently the eligibility criteria for CN patient selection has undergone re-evaluation, incorporating important determinants of adverse outcomes such as PS, number of metastatic sites, presence of nodal disease and histological sub-type [43]. Whether these factors continue to remain relevant in the era of targeted therapies remains unclear. Outcomes from the CARMENA trial may address this ambiguity and aid the development of selection criteria specific to targeted therapy.

Below is a table summarising the major randomised control studies in m-RCC

Author, study and no of participants	Study trial	Objective	Outcomes
Motzer et al, 2007 Phase III RCT 750 participants	TKI vs INF	Sunitinib vs INF α - 2b	4.6 month OS benefit Survival advantage of 26.4 months vs 21.8 months
Rini et al, 2010 Phase III RCT 732 participants	VEGFI vs INF	Bevacizumab + INF α -2b vs INF α -2b alone	0.9 month OS benefit Survival advantage of 18.3 months vs 17.4 months. Not statistically significant
Escudier et al, 2009 Phase III RCT 903 participants	TKI vs INF	Sorafenib vs placebo	3.5 month OS benefit Survival advantage of 17.8 months vs 14.3 months

Hudes et al, 2007 Phase III RCT 626 participants	mTORI vs mTORI+INF vs INF alone	Temsirolimus vs temsirolimus+ INF a- 2b vs INF α -2b alone	3.6 month OS benefit- observed only on secondary analysis of OS Survival advantage of 10.9 months vs 8.4 vs 7.3 months
Mickisch et al, 2001 Phase III RCT 85 participants	CN+INF vs INF alone	EORTC CN + INF α -2b vs INF α -2b alone	10 month OS benefit. Survival advantage of 17 months vs 7 months
Flanigan et al, 2001 Phase III RCT 246 participants	CN+ INF vs INF alone	SWOG-8949 CN + INF α -2b vs INF α -2b monotherapy	3 month OS benefit. Survival advantage of 11 months vs 8 months
Flanigan et al, 2004 Phase III RCT 331 participants	CN+ INF vs INF alone	SWOG and EORTC combined analysis	5.8 month OS benefit Survival advantage of 13.6 months vs 7.8 months
Mejean et al, ongoing Phase III RCT Recruiting	CN+ TKI vs TKI alone	CARMENA- trial CN + sunitinib vs sunitinib alone	Ongoing
Bex et al, ongoing Phase III RCT Recruiting	CN+TKI	SURTIME trial Immediate versus deferred CN + sunitinib	Ongoing

VEGFI = vascular endothelial growth factor inhibitor, mTORI = mammalian target of rapamycin inhibitor

Advances in cytoreductive nephrectomy:

Over the last two decades advancements in surgical techniques have significantly reduced post-operative morbidity rates associated with CN. Minimally invasive techniques such as laparoscopic CN (LCN) have grown in popularity since its initial description in 1991 by Clayman et al [44]. Traditionally, open nephrectomy in the setting of m-RCC was associated with significant morbidity, delaying or potentially precluding patients from receiving systemic immunotherapy which can result in disease progression, particularly CNS metastases [45]. The application of a minimally invasive approach can hasten recovery, shortening the interval before commencing therapy [46]. Furthermore, reported studies of LCN have consistently demonstrated favourable outcomes including reduced postoperative pain, shorter hospital stay and a shorter period of rehabilitation when compared to open nephrectomy. In a study from the National Cancer Institute, patients who underwent LCN had a shorter duration of recovery time, expediting the administration of immunotherapy compared with those undergoing open CN [47]. Consistent with this, data from the Cleveland Clinic concluded LCN resulted in a shorter hospital stay of 2.3 days compared to 6.1 days associated with an open approach and a notable shorter interval prior to initiation of system therapy of 36 vs 61 days [48]. In a case series of 11 patients Walther et al also described a lower analgesia requirement associated with the laparoscopic approach when compared with a similar cohort who underwent conventional open nephrectomy [49].

Overall, it appears that fears of CN precluding patients from systemic therapy may be less relevant in the era of targeted therapies and minimally invasive surgical (MIS) interventions. However, despite current evidence demonstrating superiority of MIS over open techniques, CN trials including SWOG and EORTC have only utilised open approaches. Thus further large scale randomised trials powered to compare treatment outcomes of MIS with systemic therapy are warranted.

Timing of cytoreductive nephrectomy:

Concerns over propagating metastatic disease progression by delaying targeted therapy post CN, has raised questions of commencing systemic therapy in the neo-adjuvant setting. Neoadjuvant targeted therapy paradigms are common practice for many other malignancies including those of the gastrointestinal tract, thyroid and breast [50]. Advantages of neo-adjuvant targeted therapy primarily include down-staging/sizing of an unresectable primary tumour, facilitating subsequent surgical resection with fewer complications and allowing targeted patient selection, differentiating poor responders from those exhibiting a positive clinical response or stable disease whom in turn would respond favourably to surgical resection [51]. A further advantage of delayed CN is that upon surgical resection, histology specimens may be taken to evaluate the exact biological mechanisms responsible for positive clinical response to systemic targeted therapy. This can serve to enhance our understanding of the precise mechanistic properties of targeted therapies and their effect on the progression of m-RCC [52]. Currently a retrospective study evaluating patients treated with deferred CN have higher treatment response rates when compared to immediate CN with a response rate of 12% and a median survival of 14 months compared to 8% and 12 months in the latter group [53]. Interestingly, current systemic therapy protocols are based on cytokine immunotherapy which have no biological effect on the primary tumour. It is hoped prospective randomised data collated from the SURTIME trial would shed light on the interplay of targeted therapy of delayed CN and its impact on OS and PFS [54].

Disadvantages of delayed CN include concerns that targeted therapies may potentiate surgical morbidity by obviating proangiogenic properties associated with inhibiting VEGF and other signalling pathways. This can lead to impaired microvasculature increasing the likelihood of post-operative bleeding and thromboembolic events. Furthermore these pathways play a vital role in tissue integrity with subsequent disruption leading to an increase in impaired wound healing rates and incisional hernia incidence. Withholding systemic therapy for at least 2-3 half life cycles prior or post-surgery may help preserve microvasculature and tissue integrity and reduce adverse effects. However there are no randomised studies demonstrating this and limited data exists on the safety profile of delayed CN and targeted therapy as a combined treatment strategy[55]. Retrospective data including a small case series of 19 patients undergoing delayed CN revealed this treatment paradigm to be generally safe and well tolerated with low morbidity rates. Although a larger retrospective study examining the side effect profile of delayed CN in 44 patients observed a high complication rate of 39% however most were minor and mirrored morbidity of patients undergoing initial surgical resection [56]. Overall, evidence from retrospective data support the integration of delayed CN and targeted therapies in

appropriately selected patients. Prognostic factors and PS have an important role in determining which patients are most likely to benefit from this treatment paradigm.

Role of metastectomy in m-RCC

Recently, small trials have demonstrated CN alongside metastasectomy in selected patients with low volume m-RCC positively impact on survival outcomes. A trial led by Eggener et al demonstrated surgical resection of metastatic foci yielded improved long term disease free survival in 44 patients[57]. Consistent with these findings Alt et al found the absence of complete metastasectomy was associated with significant three-fold increase risk of death with a hazard ratio of 2.91 and thus concluded complete resection of macroscopic metastases should be considered in surgically appropriate candidates [58]. Findings from a systematic review identified eight studies comparing complete metastasectomy, incomplete metastasectomy or no metastasectomy. There was a significant longer term median survival associated with complete metastasectomy compared to no metastasectomy with a median of 40.8 months versus 14.8 months respectively. Assessment of hazard ratios unequivocally favoured complete metastasectomy in all eight studies [59]. Although, current evidence favours metastasectomy as a treatment approach to m-RCC the benefit of targeted therapy use post-metastasectomy requires further evaluation.

Role of nephron sparing surgery (NSS) in m-RCC

The role of nephron sparing surgery (NSS) has recently been evaluated for the management of m-RCC in individuals where preservation of renal function is pertinent. Interestingly, a study, albeit small sample size comparing NSS with CN in patients with m-RCC found comparable survival benefit [60]. However the sample size was small and thus it would be difficult to derive clinical meaningful outcomes. A more recent study evaluating patients undergoing NSS compared to CN with renal cortical tumours, demonstrated a superior median survival advantage of 5.1 years and 3 years respectively, This advantage could partly be explained by the preservation of renal function in NSS, whereas CN can lead to deteriorating renal function and the subsequent complications associated with the development of chronic kidney disease [61].

In future it will be interesting to assess how the interplay between targeted therapies and the combination of metastasectomy and CN versus CN alone or CN versus NSS compare in response rates, PFS and OS outcomes. Notably each surgical intervention has its own eligibility criteria for patient selection which involves incorporating varying prognostic factors relevant to each modality. This in turn could be affected when combined with targeted therapy.

Role of combined targeted therapy in m-RCC

Targeting separate pathways involved in renal cell carcinogenesis have been postulated to maximise treatment outcomes allowing patients to derive the full benefits of treatment. The potential of synergistic antitumor effects with combined therapy has been evaluated in a phase I study assessing sunitinib in combination with tremelimumab an anti CTLA-4

antibody within the metastatic setting. Of 21 patients, 9 achieved a partial tumour response however it resulted in unacceptable toxic outcomes including acute renal failure and will not be further evaluated [62]. A larger prospective study of 63 patients treated with bevacizumab and erlotinib, targeting EGF revealed 25% exhibited positive treatment responses. The authors proposed the efficacy of combined treatment was superior to either drug alone, owing to targeting of multiple signalling pathways [63]. Unfortunately development of this study with the addition of imatinib to bevacizumab/erlotinib proved to increase grade 3/4 toxicities including diarrhoea, rash and fatigue [64]. Vaccines in conjunction with targeted therapies are also being explored. Findings from a phase II study evaluating a dendritic cell based vaccine AGS-003 with sunitinib compared with sunitinib monotherapy illustrate superior PFS (11.9 months versus 8 months respectively). Importantly no added toxicity was observed [65].

Overall, the potential benefit of combined treatment strategies with complementary mechanism of action support the use of targeted therapies in combination with immunotherapies, vaccines and T-cell modulating agents. Although emerging evidence of early phase clinical trials appear promising, clinicians must be mindful of the potential toxicity of combined regimens [66].

Conclusion:

CN alongside adjuvant cytokine immunotherapy is a well-established treatment protocol in the management of m-RCC, demonstrating independent significant survival advantage when compared to immunotherapy alone. Since the 1990's the introduction of tumour targeted therapies have resulted in modest improvements in patient survival when compared to cytokine immunotherapy. Advancements in surgical techniques and procedures, coupled with manipulation of targeted therapy dosing regimens and combined therapeutic strategies have further optimised treatment outcomes and prolonged OS. However current response rates have improved modestly resulting in marginal improvements in 5 year mortality rates. Furthermore PFS remains temporary with evidence of tumour progression between 6-12 months.

With continuing innovation, the role of CN within the metastatic setting will no doubt change in the foreseeable future. Whether CN continues to play a role in m-RCC management in the targeted therapy era or whether it is superseded by targeted therapy alone remains to be evaluated in randomised prospective trials. Questions will likely arise on the appropriate timing of CN and how this would affect prognostic factors used to identify surgically appropriate candidates. Current evidence based on non-randomised retrospective trials are promising however outcomes of the CARMENA and SURTIME trial are eagerly anticipated to advance this evidence base. Until then given current retrospective evidence of the beneficial role of CN alongside immunotherapy, CN should not be abandoned but still be considered as a viable therapeutic strategy in carefully surgically selected patients.

Conflict of interest:

None

Abbreviations:

RCC- renal cell carcinoma
m-RCC- metastatic renal cell carcinoma
VHL-von Hippel Lindau
EGF- epidermal growth factor
PEGF-pigment epithelial derived factor
VEGF-vascular endothelial growth factor
HIF-hypoxic inducible factor
CN-cytoreductive nephrectomy
TKI-tyrosine kinase inhibitor
m-TOR-mammalian target of rapamycin
INF- interferon
PFS-progression free survival
OS-overall survival
PS-performance status
RTC- randomised controlled trial
FPTV-fractional percentage of tumour volume removed
HRQL-health related quality of life
EORTC-European Organisation for the Research and Treatment of Cancer
SWOG-southwest oncology group
MSKCC-Memorial Sloan Kettering Cancer Centre
LDH: lactate dehydrogenase
LCN-laparoscopiccytoreductive nephrectomy
MIS-minimally invasive surgery
NSS-nephron sparing surgery

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